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SOCIETA' ITALIANA DI VIROLOGIA
ITALIAN SOCIETY FOR VIROLOGY

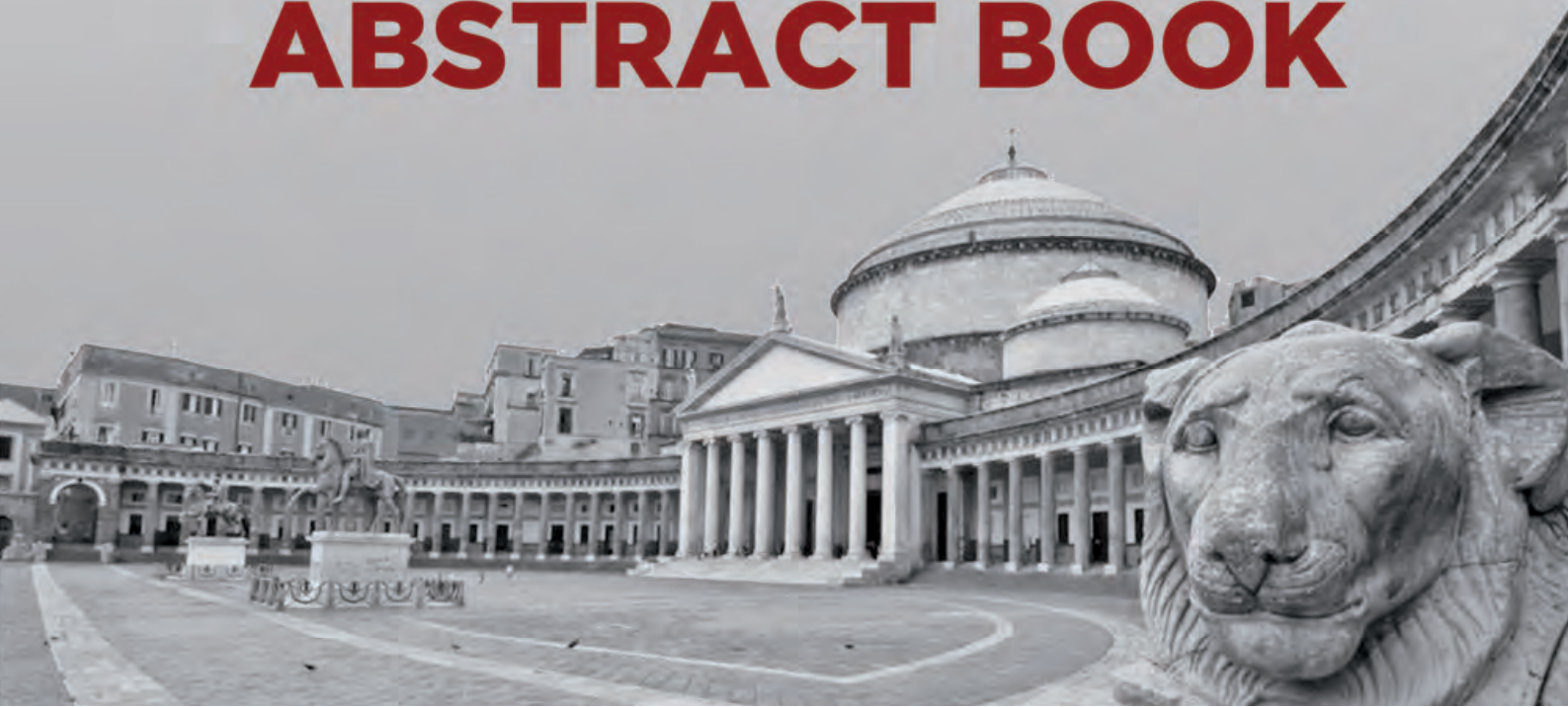
6th National Congress of the Italian Society for Virology

One Virology One Health

Naples
July 3-5, 2022

Hotel Royal Continental
Via Partenope, 38

ABSTRACT BOOK



PO 115
IDENTIFICATION OF NEW SARS-COV-2 MAIN PROTEASE INHIBITORS BY AN INTEGRATED *IN-SILICO* AND *IN-VITRO* STRATEGY

C. Salata[1*], M. Mirandola[1], C. Salaris[1], M.L. Macchia[2], E. Fornasier[3], M. Pavan[2], G. Giachin[3], A. Sosic[2], M. Sturlese[2], M. Bellanda[3], R. Battistutta[3], S. Moro[2], B. Gatto[2]

1 Department of Molecular Medicine, University of Padua, Padova, Italy
2 Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padova, Italy
3 Department of Chemical Science, University of Padua, Padova, Italy

By February 2020 SARS-CoV-2 has spread from China (Wuhan) to countless countries around the world with devastating effects for public health and global economy. In December 2020, following an unprecedented effort of the pharmaceutical industries, new vaccines able to fight SARS-CoV-2 were developed and approved for emergency use. However, the short immunological protection, vaccine hesitancy, and the continuous occurrence of virus variants limited their efficacy to control the virus circulation. At the present time, approved drugs are limited, and the development of new therapeutics is the highest valuable tool to fight this pandemic outburst.
In this view, the main protease of SARS-CoV-2, M^{pro}, is an appealing target for the development of inhibitors, due to its essential role in the viral life cycle and high conservation among different coronaviruses. Recently, it has been approved the first oral antiviral against COVID-19 (Paxlovid) based on a peptidomimetic M^{pro} inhibitor. However, the active compound suffers of a high metabolic instability and must be co-administered with Ritonavir that increases side effects.
In this prospect, the aim of the present work is the identification of novel inhibitors of SARS-CoV-2 M^{pro} to develop new and more effective lead compounds. To this end, a structure-based virtual screening was performed on a library of commercially available compounds, followed by FRET-based screening, biophysical and crystallographic analyses on the isolated recombinant target. Ten hits - including covalent and not-covalent M^{pro} inhibitors with different chemical scaffolds - were selected for the evaluation of antiviral activity by a phenotypic cell-based assay. Six out of the ten hits protected Vero E6 cells from SARS-CoV-2-induced cytopathic effects confirming their antiviral activity. At the moment, further assays are ongoing on different cell lines to validate and characterize the antiviral activity of the hits. These good preliminary results might pave the way to discover novel inhibitors that could lead to the development of clinically relevant inhibitors.

Acknowledgments. *This work was supported by funding from the CARIPARO Foundation 'Progetti di ricerca sul COVID-19' No. 55812.*